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(54) HIV-2 virus variants.

(57) HIV-2 virus variants, namely virus HIV D194 and virus HIV D205, which can be cloned from the corresponding virus isolate HIV D194 (ECACC V 87122303) or from the infected cell line HUT 194 (ECACC V 87122306) or from the virus isolate HIV D205 (ECACC V 87122304), respectively, and their RNA or RNA-fragments and DNA and DNA-fragments derived therefrom and/or proteins and the use thereof for diagnostics and therapy.

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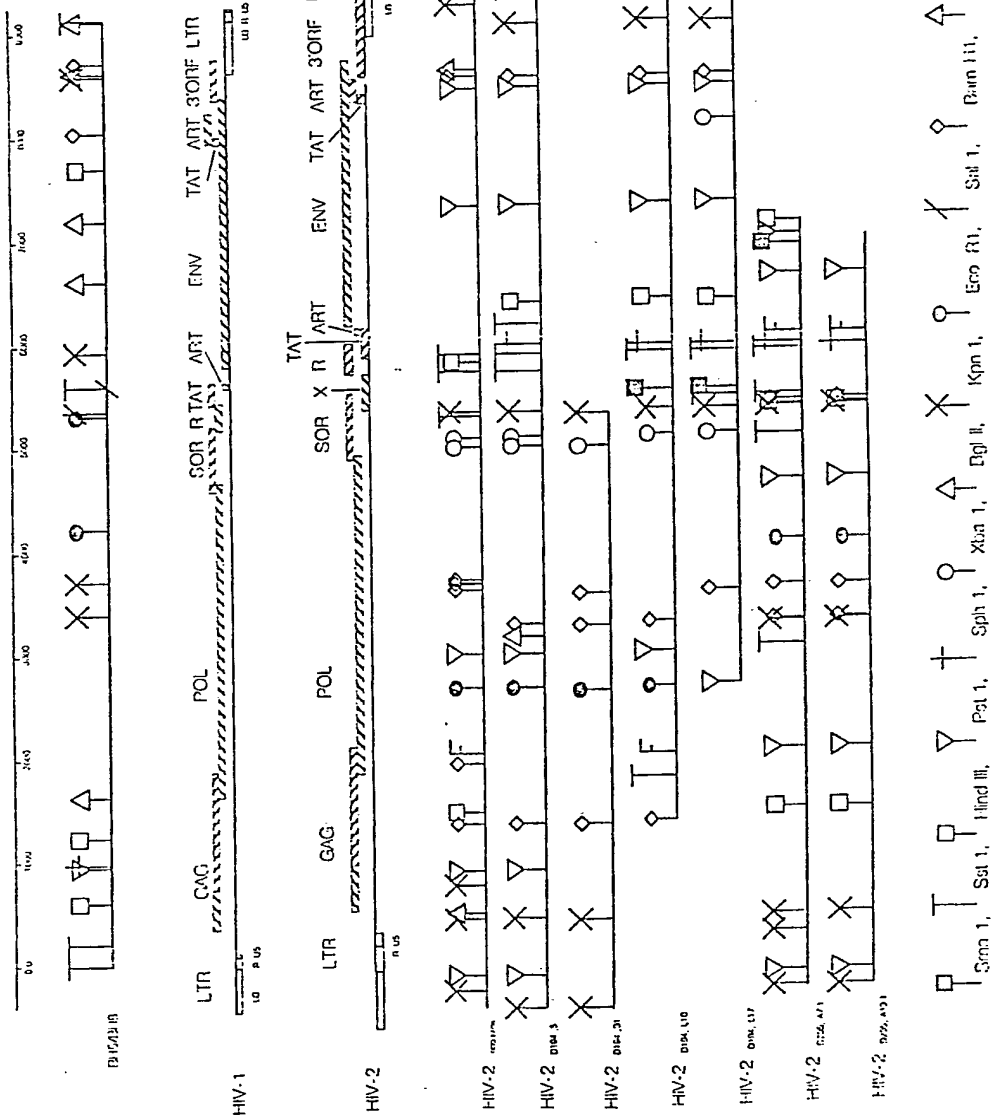
Fig. 2



Description

HIV-2 VIRUS VARIANTS

The present invention relates to HIV-2 virus variants, namely Virus HIV D194 and HIV D205 that may be cloned from the corresponding virus isolate HIV D194 (ECACC V 87122303) or from the infected cell line HUT 194 (ECACC V 87122306) and from the virus isolate HIV D205 (ECACC V 87122304), respectively, and to the RNA or RNA-fragments and derived therefrom DNA and DNA-fragments and/or proteins and the use thereof for diagnostics and therapy.

"Molecular cloning of two West African human immuno-deficiency virus type 2 isolates which replicate well on macrophages: a Gambian isolate from a case of neurologic aquired immunodeficiency syndrome, and a highly divergent Ghanesian isolate" (Kühnel, H., v. Briesen, H., Dietrich, U., Adamski, M., Mix, D., Biesert, L. Kreutz, R., Immelmann, A., Henco, K., Meichsner, Ch., Andreesen, R., Gelderblom, H. & Rübsamen-Waigmann, H., 1989, Proc. Natl. Acad. Sci. 86, 4, 2383-2387.

In diagnostics, two criteria are demanded to be met, namely specifity and sensitivity for the antigen to be detected. In the diagnostics of AIDS the demand for specifity can certainly be complied with by using the isolates HTLV-III_B and LAV-2 (Guyader, M. et al., "Nature" 326, 1987, 662-669) in order to delimit HIV infections from other infections and, thus, to make a rough assignment into the classes of "HIV-2-related infections" or "HIV-1-related infections". However, a problem is constituted by the sensitivity of the diagnosis. In the range of the so-called seroconversion, i.e. the initial occurrence of the antibody in the infected person, a reduction in sensitivity implies an increase in the number of "falsely negative" test results. Accordingly, it is one main goal to shorten the period between an infection and the detectability of this infection as much as possible by improving the test sensitivity.

A decreased cross reactivity, in the practice of the widely employed ELISA diagnostics, is manifested, for example, in a reduced sensitivity. Thus, the use of the described HIV-1 isolate means about an average reduction of the test sensitivity against HIV-2 sera by the factor of 100 to 1000, whereas the isolate HTLV-III_B enables almost no detection to be accomplished anymore.

A disastrous principle of the diseases caused by HIV resides in the fact that there is not only one type of each of HIV-1 and HIV-2 virus phenotypes and genotypes. What is to be premised is rather a large group of related viruses, possible even populations which by no way are strictly separated from each other but continuously penetrate one another and undergo some evolutionary development to a more and more increasing divergence, while at the same time they begin by recombination events to exchange between each other parts of the genom. Thus, the existing HIV species form a broad continuous population level in which there are no narrowly delimited subpopulations of one virus variant. There is rather to presumed that a continuum exists which is subject to permanent fluctuations with time.

The classified virus variants HIV-1 and HIV-2 are representatives of the diffusely delimited subpopulations having a relative low degree of relationship, which is manifested by only a partial cross reactivity. On the other hand, there are variants of the HIV-1 group (Rübsamen-Waigmann, H. et al., "AIDS-Forschung" 10, 1987, 572-575; Rübsamen-Waigmann, H. et al., J. Med. Virol. 19, 1986, 335-344; v. Briesen, H. et al., J. Med. Virol. 23, 1987, 51-66), which do significantly stronger cross-react with HIV-2 than the first characterized HIV-1 isolate itself (Hahn, B. et al., "Nature" 312, 1984, 166-169). A commercial product consisting of such an isolate diagnoses distinctly more sera as being HIV-2 positive than does the described standard isolate HTLV-III_B.

An ideal diagnostic or therapeutic product should contain at least one representative from the populations as significantly biologically distinguished from one another.

HIV-1 viruses in a multitude of highly polymorphic genetic mutants may cause different diseases such as ARC, LAS, AIDS and encephalopathies (ARC: AIDS-related complex, LAS: lymphadenopathy syndrome, AIDS: acquired immune deficiency syndrom). Cloned virus variants are distinguished in sequence and restriction pattern, even if they have been isolated at the same time, at the same place and even from the same patient (Rübsamen, H. et al., 1986). It could be shown that virus variants of the HIV-1 type are distinguished in some virus antigens up to about 15%. HIV-2's are even different in more than 40% of the aminoacids in some antigens, substitutions, insertions and deletions having been considered (Guyader, M. et al., 1987; Rabson, A.B. & Martin, M.A. "Cell" 40, 1985, 477-480).

The present invention provides two variants of the HIV-2 virus. One variant was isolated from a clinically asymptomatic patient, and one variant was isolated from a patient suffering from terminal so-called neuro-AIDS. The virus isolates proved to be diagnostic agents, relative to DNA/RNA as well as relative to the virus antigens, for serologically and directly identifying infections by the type HIV-2 in the pre-AIDS and AIDS stages.

The virus isolates according to the invention comprise viruses and proviruses, the characteristics of which are identical to those of the disclosed restriction map and the sequence of the cloned partial regions (Figures, 2-8). Moreover, the virus isolates comprise variants which are distinguished from the viruses and proviruses described above in that they are different in their nucleotide sequences from the above-described viruses only by up to 5%, and preferably by 2%, particularly preferred by 1%.

The virus variants according to the invention may cause lymphadenopathies (further designated as LAS/AIDS) or serious neurological disorders (encephalopathies). Claimed according to the invention are also expression products of said virus variants, and more particularly antigens, preferably in accumulated or pur

form, and processes for producing said expression products in full or in parts or in combinations of the parts. The expression products are intend d to include all polypeptides in glycosylated and or meristylated forms which have been coded on the positive or negative strand of the cloned RNA or DNA.

A further preferred embodiment consists of cloned DNA sequences capable of hybridizing with genomic RNA and DNA of the virus variants. Claimed according to th invention are stable gen probes containing such DNA sequences which are suitable for the detection of hybridization of those and other HIV variants or related viruses or DNA proviruses in samples to be investigated, more particularly biological or semi-synthetic samples.

A further preferred embodiment of the invention is comprised by virus variants the RNA/DNA of which or respective fragments will hybridize to the virus variants according to the invention under stringent conditions, more particularly c-DNA, genomic DNA, recombinat DNA, synthetic DNA or fragments thereof. These are understood to include variants or fragments which exhibit deletions and insertions in comparison to the virus variants according to the invention.

Stringent conditions of hybridization and washing are meant to be understood as those conditions which ensue by way of experiment or calculation if the melting point of the 100% homologous nucleic acid complexes in conditions of hybridization and washing will be fallen below by not more than 5 °C under the buffer conditions employed.

Also claimed according to the invention are cloned synthetic gen probes which may be derived from the above-described virus variants and can be augmented in vector systems in eukaryotes or prokaryotes. The described cloned DNA fragments are suitable for hybridization with complementary nucleic acids (DNA/RNA) for the purpose of diagnostic detection of the virus variants. The diagnostic tests according to the invention are carried out by using DNA or RNA probes. The probes are radioactive or have been labelled with fluorescent bio- or chemiluminescent groups or enzymes or are specifically detectable with enzymes via coupled reaction systems. The hybridizations may be effected in a homogeneous phase of a solution or in a heterogeneous phase with solid-immobilized nucleic acids, while the solid may be a membrane, particle, cell or tissue, so that the hybridization may also be effected in situ.

From the virus isolates claimed according to the invention, the corresponding DNA sequences (Figure 2) may be cloned in E. coli bacteria by establishing a genomic lambda-gen bank, starting from the DNA of the lymphocytes infected with the virus isolate. The desired clones are obtained by carrying out a plaque-screening with STLV-III sequences of the gag-pol range. In a more specifical way, there may be used as a probe a DNA derived from the published sequence HIV-2 ROD (Guyader, M. et al., "Nature" 326, 1987, 662-669), or a DNA probe derived from the partial sequences of the isolates HIV-2 D194 and HIV-2 D205 according to the invention. Thus from Figure 3 a probe may be derived which under stringent conditions will hybridize only with variants of the type HIV-2 D194, however not with variants of the type HIV-2 ROD.

The diagnostic method based on the use of the viruses claimed according to the invention comprises the following steps: Extraction of RNA or DNA from biological samples, possibly enzymatic processing by restriction enzymes, separation by gel electrophoresis and/or direct blot methods for nucleic acid-binding carriers, and subsequent hybridization with parts of the cloned fragments of the claimed viruses. Hybridizations may also be directly carried out in chemically treated cells or tissues. Therein the origin of the tissues or liquids is insiginificant.

Specifically, a process for the in vitro detection of antibodies against expression products of the viruses of the present invention is characterized in that the expression products or parts thereof of the viruses are detected by means of immunological methods. The process is characterized in that the expression products are proteins, peptides or parts thereof which have been coded within the meaning of an open reading frame on the DNA of the proviral partial sequences as characterized in claim 1 and are prepared by synthetic or biosynthetic processes.

The process is further characterized in that previously a definite amount or a combination of expression products or parts thereof are fixed on microtiter plates, whereupon subsequently biological samples, diluted or undiluted, are contacted with the coated microtiter plates and after incubation and sequential washing steps can be identified by means of a detecting reagent or of labelled anti-HIV antibodies.

Alternatively, filter strips and plastic strips or rods are used instead of microtiter plates, wherein the expression products of the viruses have been fixed at respective specific positions by isolated application of the different antigens.

The expression products or parts thereof can also be separated by gel electrophoresis and then transferred by blotting whereupon incubation with anti-HIV antibodies and the detection thereof are effected. Detection is effected on solid phase carriers to which the antigen determinants have been bonded, with the solid phase carrier consisting of particles.

Expression products can be virus antigens derived from in vitro-infected cells, said antigens being contacted with biological test materials as antigens bonded to fixed cells, and that the subsequent antibody bonding can be determined with immunological detection reagents by means of an apparatus, for example with a cytofluorimeter, or visually.

The antigens can be determined by competitive ELISA. HIV-related nucleic acids (DNA and RNA) can be detected in biological samples, cells and in isolated form by using the nucleic acids according to the present invention.

Expression products can be supplemented by materials which are related to other HIV variants, which,

however, are distinguished in their biological properties from the materials of the isolates of the present invention.

For diagnostic and therapeutic goals the described DNA segments may also be employed for expressing coded antigens, parts thereof or combinations thereof with ali n antigens. Therein the DNA segments under aimed control of regulation sequences are introduced into pro-or eukaryotic target cells, tissues or multiple-cell organisms to stimulate these to produce the accordingly coded antigens, parts thereof or combinations thereof with alien antigens. Antigens can be detected via the reaction with Anti-HIV-2 antibodies, more particularly from the sera of the respective patients. Antigens having longer open reading frames (> 50 amino acids) lend themselves as well those which are subject to splicing processes on the RNA level and are only thus composed to form the longer open reading frames.

According to the invention further claimed are polypeptides originating from the cloned virus variants according to the invention to detect such antigens in the material under investigation which contain similar antigen determinants and thereby do immunologically cross-react. This is particularly suitable for the diagnosis of AIDS and pre-AIDS of virus carriers or asymptomatic virus carriers or virus products, respectively, which are derived from blood. Also the serological detection of the antibodies directed against these antigenic polypeptides as expression products of the viruses claimed according to the invention becomes possible by employing conventional systems such as ELISA. The immunogenic polypeptides may be used as protective polypeptides as vaccines to cause protection against AIDS infections.

The polypeptides according to the invention are understood to include fragents which are intentionally obtained by means of gen-technological methods, starting from longer open reading farmes as well as those obtained by proteolytic enzymes in the production bacterial starins or in vitro by the use of proteases.

The virus isolates according to the invention and the products derived therefom may be combined with other isolates of the partial population HIV-2 in test systems, that is with those which are as far remote as possible in the described population level such as for example, the isolate HIV-2 ROD (Guyader, M. et al., 1987). Thereby it becomes possible sensitively to detect also populations of remote relationship in one test.

The virus variants according to the invention are highly different from the spectrum of the HIV-1 variants and have a closer molecular relationship to the HIV-2 virus described by Guyader, although they are distinguished therefrom to a significant extent (Figure 1, Figure 2, Figure 3). Also the biological properties are clearly distinguished from the described HIV-2 isolate. Thus, the variants according to the invention, for the effective in vitro replication, prefer cells which are derived from myeloidic lines. On the contrary, the virus poorly reproduces itself on lymphocytic lines. This quality especially refers to HIV-D194.

The virus HIV D194 according to the invention exclusively caused encephalopathic symptoms in the infected patient, due to which the patient also deceased after an extremely short time and after a fulminant progress of the disease. Samples of the viruses claimed according to the invention have been deposited in the forms of their isolates at the European Collection of Animal Cell Cultures under the designations HIV D194 (Accession No. V 87122303) and HIV D205 (V 87122304), respectively, according to the Budapest Treaty.

A cell line infected with the virus isolate HIV D194 has been deposited under the designation HUT 194 (ECACC V 87122306) at the above-identified Deposit.

Figure 1 shows the deviation of the proteins p24 and gp41 from lambda D194 and HIV-2 ROD 27/35 in its nucleotide sequence and amino acid sequence (Guyader, M. et al., 1987, Nature 326, pages 662 - 669).

Figure 2 shows the restriction maps of the virus isolates according to the invention in comparison to known HIV sequences.

Figure 3 shows a comparative section of a sequence between HIV-2 ROD (Guyader, M. et al., 1987) and HIV-2 D194, which demonstrates the significant divergence of the variant HIV-2 D194 according to the invention in a coding range of the envelope protein gp120.
The section of the sequence shows a range of the gp120 region in comparison to the nucleotide sequence and the corresponding amino acid sequence in the single letter notation between HIV-2 D194 and HIV-2 ROD (Guyader, M. et al., 1987). The indication of the position refers to HIV-2 ROD. (-) symbolizes deletions/insertions. (.) symbolizes identical nucleotides.

Figure 4 shows a nucleotide sequence, characterizing the clone HIV-D194. Nucleotide positions designated as N or O could not be unambiguously derived from the gel pattern. The sequence starts with R/U5 region the LTR and ends with U5 region. The sequence shown is derived from subclone L10 (see restriction map). This clone differs from others derived from the same patient/blood sample by around 1 % in the nucleotide sequence as it was determined by comparison with 5kb homologous sequences derived from clone HIV-194,5.

Figure 5 shows the partial nucleotide sequences of HIV-D205 (corresponding to clone HIV-2 A7.1 of Figure 2).

Figure 6 shows the sequence homology between HIV-D194 and HIV-2 ROD in (%), separately for the functional elements.

Figure 7 shows the sequence homology of HIV-2 D205,7 compared to the HIV/SIV group (gene level; nt/aa).

Figure 8 shows a nucleotide sequence comparison of HIV-2 D205 with HIV and SIV strains (in % homology).

Figure 9 shows the correspondence of the op n reading frames with functionally known antiviral antigens.

Figure 10 shows the primer mediated constructions which are inserted as corresponding restriction fragments into the appropriate vectors.

Experimental results and characteristics of HIV-D194 and HIV-D205 are described in Kühnel, H. et al. (1989) Proc. Natl. Acad. Sci. 86, 4, 2383-2387.

The sequence of HIV-D194 shows a lot of so-called "open reading frames" as the fragments of HIV-D205 do. Most of these reading frames can be related to in vivo expressed proteins/antigens by comparison of homologies to previously described HIV-viruses, by comparison of Western blots performed with HIV-D194 and HIV-D205 antigens derived from infected HUT78 or U937 cells and by probing with sera from the corresponding patients and reference sera. Figure 9 shows the correspondence of the open reading frames (numbers refer to Figure 4 and 5) with functionally known antiviral antigens.

Other open reading frames are not identified on the level of their expressed antigens defined by function or antibody staining on Western Blot. However, they can be expressed under some circumstances in vivo. Other leading frames, even short ones, can be expressed as well in a way difficult to predict solely on the basis of nucleic acid sequencing data because of splicing processes.

Antigenic determinants on expressed proteins as they are important for the biological function, for target antigens in diagnostics or for immunization are spread all over the expressed linear protein sequence. Parts of these sequences can have more general antigenic properties than others as can be shown by peptide screening/mapping for antigenic sites. These sites can be expressed as single epitopes or as continuous polypeptide or in a version of in vitro or synthetically spliced antigens. Antigenicity of the expressed products can be demonstrated by antigen fixation and blotting in the Western Blot assay. Constructions for antigen expression in E. coli can be done by using conventional techniques using synthetic genes, restriction fragments from cloned viral genome segments, trimming products thereof by using exonuclease or DNase I or by using sequence specific synthetic primers (Figure 10) defining the desired 5′ and 3′ end of the fragment to be expressed together with appropriate restriction sites. These restriction sites can easily be used for ligation into a panel of expression vectors of different organisms like those derived from PLc24 (Remault et al. 1981 Gene 15, 81-83) with multicloning sites (pEX).

The expressed antigens were shown to specifically react with patients' sera. The p27(24) from gag of HIV-D205 react very sensitively with both typical HIV-1 sera and typical HIV-2 sera (see Kühnel et al). The antigenic sequence corresponding to the region shown in Figure 3 is highly specific for this particular subfamily of HIV-variants.

EXAMPLE 1

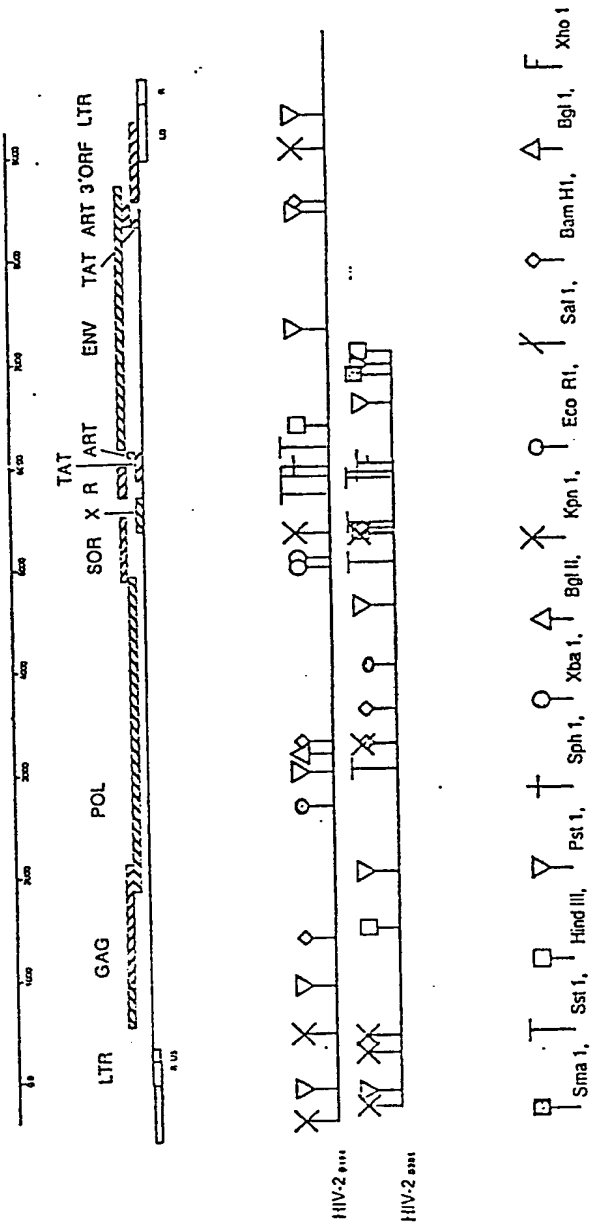
Cloned subfragments such as the Kpn-Kpn fragment comprising the gag-pol region of HIV-D194 are used as probes for HIV-2 type and SIV type sequences by hybridizing under conditions 30-40° C less in hybridization and washing conditions appropriate for homologous sequences.

HIV-1 sequences do not show up in blot and in situ hybridization unambiguously, although this region contains the p24/27 coding region which heavily cross-reacts with anti HIV-1 sera. A nucleic acid probe such as shown in and corresponding to Figure 3, however, highly specifically detects the specific subfamily of HIV-D194 compared to all other known HIV isolates. This is shown by in situ hybridization using run-off RNA of this particular region.

Claims

1. A virus isolate HIV D194 (ECACC V 87122303) and a virus isolate HIV D205 (ECACC V 87122304).

2. DNA of the proviral partial sequences according to the following restriction endonuclease section-site characteristics, within the scope of the possible and conventional variation of errors, formed in establishing restriction maps.



3. cDNA and -fragments of the virus isolates according to claim 1.

4. Viral RNA and its fragments from virus isolates according to claim 1.

5. Recombinant DNA containing DNA pieces, starting from the virus isolates according to claim 1.

6. DNA or RNA of the virus isolates according to any one of the claims 1 to 4, wherein the DNA or RNA is present as hybride with complementary labelled DNA or RNA strands.

7. DNA according to any one of the claims 1 to 5, characterized in that it is complementary to viral DNA or parts thereof.

8. Nucleic acid strands in a modified or unmodified form which under stringent conditions hybridize with nucleic acids according to claims 2 to 7, and more specifically those nucleic acids which correspond to the highly variable regions of the HIV genom, more particularly in the range of the region coding the envelope protein.

9. Expression products of the virus isolates according to claim 1.

10. Expression products according to claim 1, characterized in that the proteins, peptides or fragments have been coded within the meaning of an open reading frame on the DNA according to claim 2.

11. A process for the in vitro detection of antibodies against expression products of the viruses according to claim 1, characterized in that the expression products or parts thereof of the viruses are detected by means of immunological methods.

12. The process according to claim 11, characterized in that the expression products are proteins,

peptides or parts thereof which have been codes within the meaning of an open reading frame on the DNA according to claim 2 and are prepared by synthetic or biosynthetic processes.

13. The process according to claims 11 or 12, characterized in that previously a definite amount or a combination of expression products or parts thereof are fixed on microtiter plates, whereupon subsequently biological samples, dilut d or undiluted, are contacted with the coated microtiter plates and aft r incubation and sequential washing steps can be identified by means of a det cting reagent or of labelled anti-HIV antibodies.

14. The process according to one of claims 11 to 13, characterized in that filter strips and plastic strips or rods are used instead of microtiter plates, wherein the expression products of the viruses have been fixed at respective specific positions by isolated application of the different antigens.

15. The process according to claim 14, characterized in that the expression products or parts thereof are separated by gel electrophoresis and then transferred by blotting whereupon incubation with anti-HIV antibodies and the detection thereof are effected.

16. the process according to any one of claims 11 to 15, characterized in that the detection is effected on solid phase carriers to which the antigen determinants have been bonded. the solid phase carrier consisting of particles.

17. The process according to any one of claims 11 to 16, characterized in that the expression products are virus antigens derived from in vitro-infected cells, said antigens being contacted with biological test materials as antigens bonded to fixed cells, and that the subsequent antibody bonding can be determined with immunological detection reagents by means of an apparatus, for example with a cytofluorimeter, or visually.

18. The process according to one of claims 11 to 17, characterized in that the antigens are determined by competitive ELISA.

19. A process for detecting HIV-related nucleic acids (DNA and RNA) in biological samples, cells and in isolated form by using the nucleic acids according to claims 2 to 7.

20. The process according to any one of claims 11 to 19, characterized in that the expression products are supplemented by materials which are related to other HIV variants, which, however, are distinguished in their biological properties from the materials of the isolates according to claim 1.

21. Immunogenic composition, containing expressing products such as antigens, codes by the viruses of the virus isolates according to claim 1.

22. The immunogenic composition according to claim 21, characterized in that one antigen constitutes part of the total membrane antigen or is the total membrane antigen or a derivative thereof or a mixture of parts of the membrane antigens.

23. Antibodies, and more specifically monoclonal antibodies, against expression products of the virus isolates according to claim 1.

24. Cells which have been transformed with nucleic acids according to any one of claims 2 to 7.

25. Cells which have been infected with virus isolates according to claim 1.

26. Cell line HUT 194 (ECACC V 87122306).

Deviation of p24 and gp41 from lambda D194 and HIV-2 ROD 27/35*

	Nucleotide Sequence	Amino Acid Sequence
gp41	about 15%	about 21%
p24	about 13%	about 8%

* M.Guyader et al. 1987, Nature 326, 662-669

Fig. 1

Fig. 2

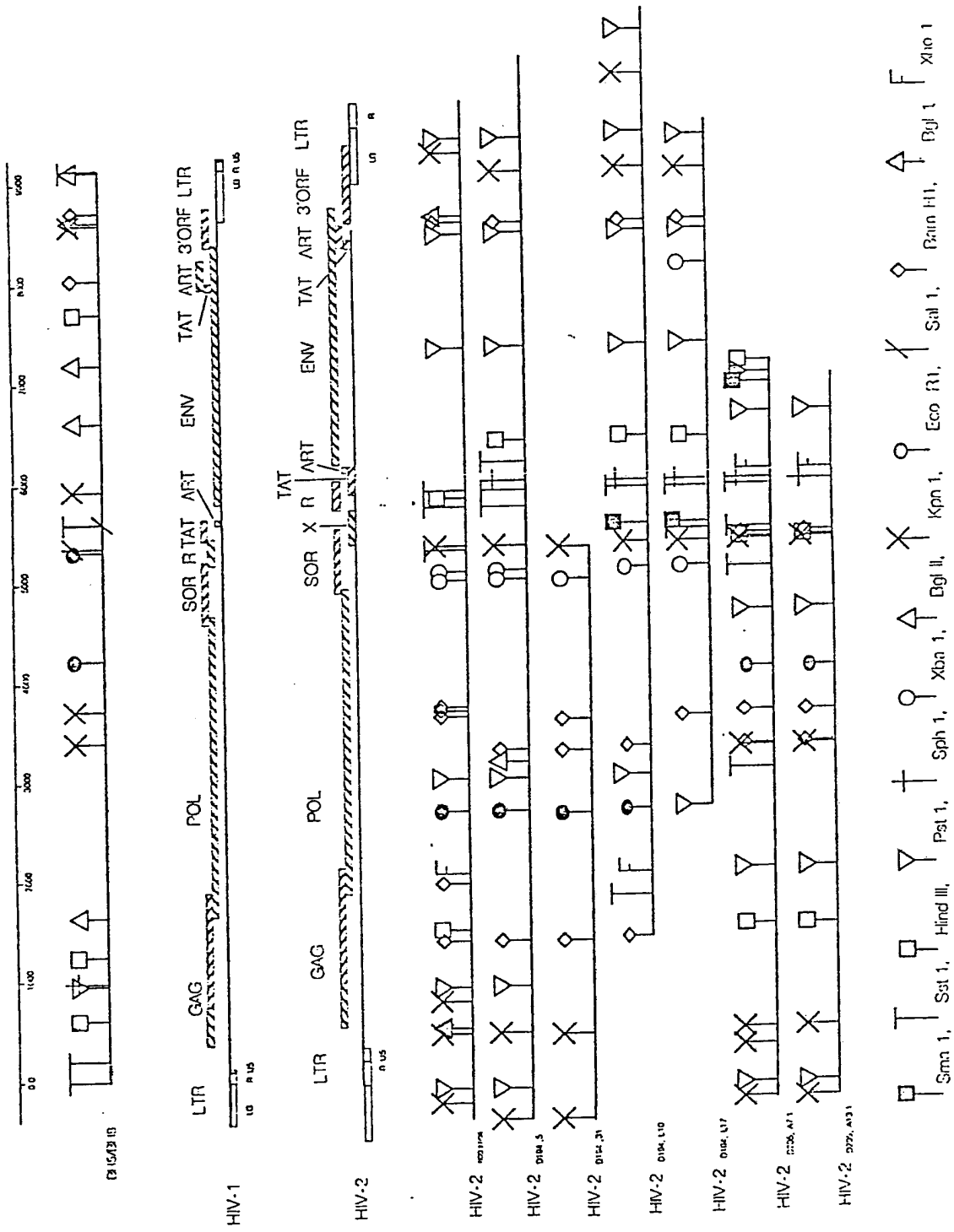
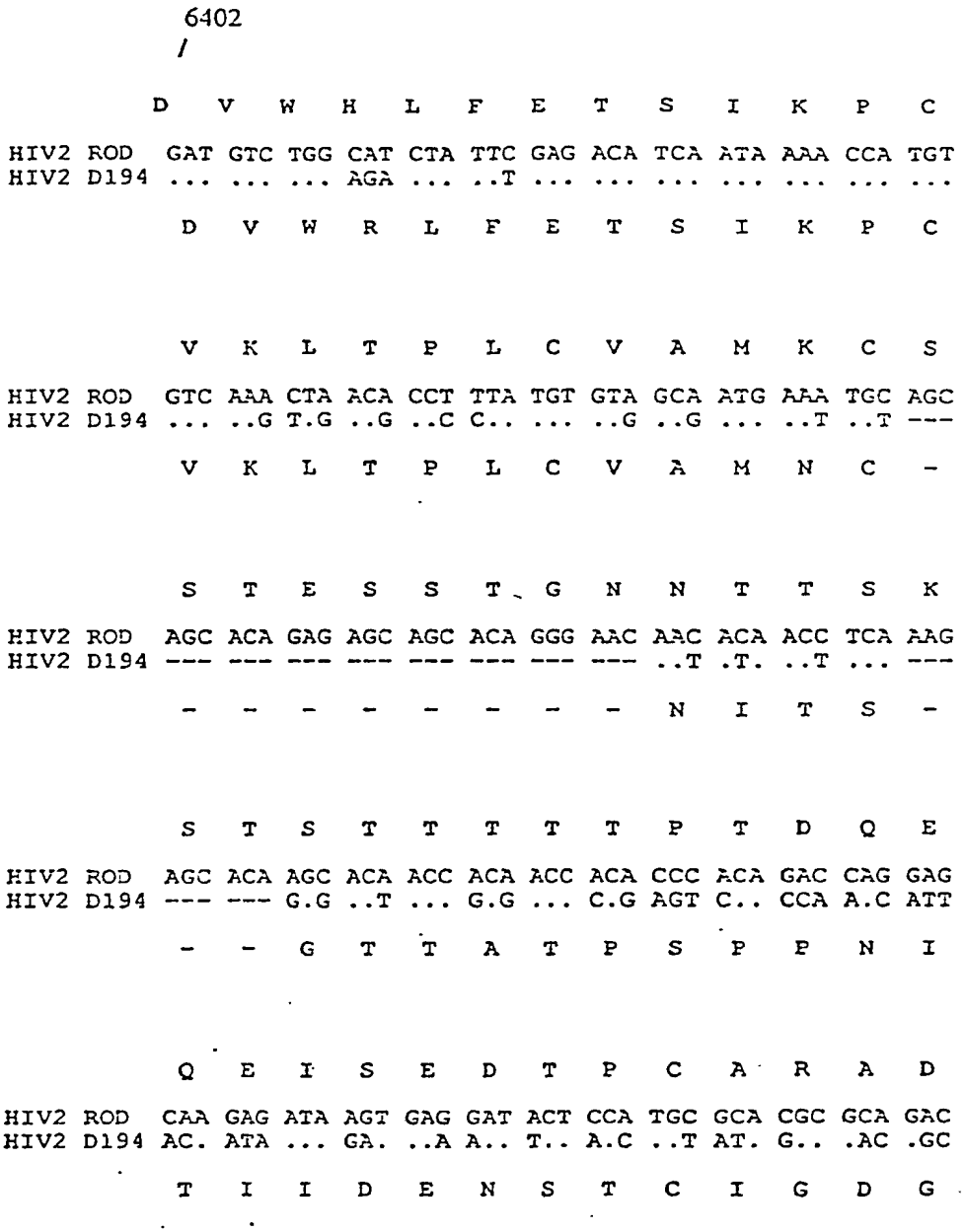


Figure 3



The section of the sequence shows a range of the gp120 region in comparison to the nucleotide sequence and the corresponding amino acid sequence in the single letter notation between HIV-2 D194 and HIV-2 ROD (Guyader, M. et al., 1987). The indication of the position refers to HIV-2 ROD. (-) symbolizes deletions/insertions. (.) symbolizes identical nucleotides.

Fig. 4.

This nucleotide sequence characterizes the clone HIV-D194. Nucleotide positions designated as N or O could not be unambiguously derived from the gel pattern. The sequence starts with the R/U5 region the LTR and ends with the U5 region.

```
                                                                      60
          10         20         30         40         50
AGTCGCTCTG CGGAGAGGCT GGCAGATTGA GCCCTGGGAG GTTCTCTCCA GCACTAGCAG

                                                                     120
          70         80         90        100        110
GTAGAGCCTG GGTGTTCCCT GCTAGACTCT CACCAGTGCT TGGCCGGCAC TGGGCAGACG

                                                                     180
         130        140        150        160        170
GCTCCACGCT TGCTTGCTTA AAGACCTCTT AATAAAGCTG CCAGTTAGAA GCAAGTTAAG

                                                                     240
         190        200        210        220        230
TGTGTGTTCC CATCTCTCCT AGTCGCCGCC TGGTCATTCG GTGTTCATCT GAGTAACAAG

                                                                     300
         250        260        270        280        290
ACCCTGGTCT GTTAGGACCC TTCCCGCTTT GAGAATCCAA GGCAGGAAAA TCCCTAGCAG

                                                                     360
         310        320        330        340        350
GTTGGCGCCC GAACAGGGAC TTGAAAGAGG ACTGAGAAGC CCTGGAACAC GGCTGAGTGA

                                                                     420
         370        380        390        400        410
AGGCAGTAAG GGCGGCAGGA ACAAACCACG ACGGAGTGCT CCTAGAAAAG CGCGGGCCGA

                                                                     480
         430        440        450        460        470
GGTACCGAAG CGGCGTGTGG AGCGGGAGTG AAAGAGGCCT CCGGGTGAAG GTAAGTACCT

                                                                     540
         490        500        510        520        530
ACACCGAAAA CTGTAGCCAG AAAAGGCTTG TTATCCTACC TTTAGACAGG TAGAAGATTG

                                                                     600
         550        560        570        580        590
TGGGAGATGG GCGCGAGAAA CTCCGTCTTG AGAGGGAAAA AAGCAGACGA ATTAGAAAAA

                                                                     660
         610        620        630        640        650
GTTAGGTTAC GGCCCAACGG AAAGAAAAGA TACAGGTTAA AACATGTTGT GTGGGCAGCG

                                                                     720
         670        680        690        700        710
AATGAATTAG ACAGATTCGG ATTGGCAGAG AGCCTGTTGG AATCAAAAGA AGGTTGCCAA

                                                                     780
         730        740        750        760        770
AAGATTCTTA AAGTTTTAGA ACCATTAGTA CCAACAGGGT CAGAAAATTT AAAAAGCCTT

                                                                     840
         790        800        810        820        830
TTTAATACCG TCTGCGTCAT TTGGTGCTTG CACGCAGAAG AGAAAGTGAA AGATACTGAA

                                                                     900
         850        860        870        880        890
GAAGCAAAGA AACTAGCACA GAGACATCTA GTGGCAGAAA CAGGAACTGC AGAGAAAATG

                                                                     960
         910        920        930        940        950
CCAAATATAA GTAGACCAAC AGCACCACCT AGTGGGAAAG GGAGGAAACT TCCCCGTGCA

                                                                    1020
         970        980        990       1000       1010
ACAGGCAGGC GGCAACTATA TCCATGTGCC GCTGAGCCCC CGAACTCTAA ATGCTTGGGT

                                                                    1080
        1030       1040       1050       1060       1070
AAAATTAGTA GAGGAAAAGA AGTTCGGGGC AGAAGTAGTG CCAGGATTTC AGGCACTCTC

                                                                    1140
        1090       1100       1110       1120       1130
AGAAGGCTGC ACGCCCTATG ATATCAATCA AATGCTTAAT TGTGTGGGCG ATCACCAAGC
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Fig. 4 Sheet 2

```
      1150       1160       1170       1180       1190       1200
AGCTATGCAA ATAATCAGAG AAATTATTAA TGAGGAAGCA GCAGATTGGG ATGCGCAGCA

      1210       1220       1230       1240       1250       1260
CCCAATACCA GGCCCCTTAC CAGCAGGGCA GCTTAGAGAC CCAAGGGGGT CTGACATAGC

      1270       1280       1290       1300       1310       1320
AGGAACAACA AGCACAGTAG ATGAACAGAT CCAGTGGATG TATAGGCAAC CAAATCCCGT

      1330       1340       1350       1360       1370       1380
GCCGGTAGGG AACATCTACA GGAGATGGAT CCAGATAGGG CTACAGAAAT GTGTCAGGAT

      1390       1400       1410       1420       1430       1440
GTACAACCCA ACTAACATCT TAGATGTGAA GCAGGGACCA AAAGAATCGT TCCAGAGCTA

      1450       1460       1470       1480       1490       1500
TGTAGACAGA TTCTACAAAA GCCTAAGGGC AGAACAAACA GACCCGGCTG TAAAAAATTG

      1510       1520       1530       1540       1550       1560
GATGACCCAA ACGCTGCTAA TACAGAATGC CAACCCAGAC TGCAAGTTAG TATTAAAAGG

      1570       1580       1590       1600       1610       1620
ACTAGGGATG AATCCCACCC TAGAGGAGAT GCTGACTGCC TGCCAGGGAG TAGGCGGACC

      1630       1640       1650       1660       1670       1680
AAGCCAGAAA GCCAGACTAA TGGCTGAAGC CCTAAAGGAG GCTTTGACGC CAGCCCCTAT

      1690       1700       1710       1720       1730       1740
CCCATTTGCA GCAGCCCAAC AAAGAAGGGC AATTAGGTGT TGGAATTGTG GAAAGGAGGG

      1750       1760       1770       1780       1790       1800
ACACTCGGCG AAACAGTGCC GAGCACCCAG AAGACAGGGC TGCTGGAAGT GTGGCAAGTC

      1810       1820       1830       1840       1850       1860
AGGACACATC ATGGCAAACT GCCCGGAAAG ACAGGCAGGT TTTTTAGGGA TGGGCCCACG

      1870       1880       1890       1900       1910       1920
GGGAAAGCAG CCCCGCAACT TCCCCGCGGC CCAAGCTCCT CAGGGGCTGA TACCAACAGC

      1930       1940       1950       1960       1970       1980
ACCCCCAATA GATCCAGCAG TGGACCTGTT GGAGAAATAT ATGCAGCAAG GGAGAAAGCA

      1990       2000       2010       2020       2030       2040
GAGAGAGCAG AGGGAGAGAC CATACAAGGA CGTGACGGAG GACTTACTGC ACCTCGAGCA

      2050       2060       2070       2080       2090       2100
GGGAGAGACG CCCCACAGAG GGGCGACAGA GGACTTGCTA CACCTCAATT CTCTCTTTGG

      2110       2120       2130       2140       2150       2160
AAAAGACCAG TAGTCACAGC ATTCATCGAG GATCAGCCGG TAGAAGTCTT ACTAGACACA

      2170       2180       2190       2200       2210       2220
GGAGCTGATG ACTCAATAGT AGCAGGAATA GAGTTAGGGG ACAATTACAC TCCAAAAATA

      2230       2240       2250       2260       2270       2280
GTGGGGGGAA TAGGGGGATT CATAAATACC AAAGAATATA AAAATGTAGA AATAAAGGTA

      2290       2300       2310       2320       2330       2340
CTAAATAAAA GAGTAAGAGC CACCATAATG ACAGGAGATA CCCCAATCAA CATTTTTGGC
```

Fig. 4


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      2350       2360       2370       2380       2390       2400
AGAAATATTC TGGCAACCTT AGGCATGTCA TTAAACCTAC CAGTCGCCAA GTTAGACCCA

      2410       2420       2430       2440       2450       2460
ATAAAAGTAA CATTGAAGCC AGGGAAAGAT GGACCAAGGC TGAAACAATG GCCCCTAACA

      2470       2480       2490       2500       2510       2520
AAAGAAAAAA TAGAAGCACT AAAAGAAATT TGTGAAAAAA TGGAAAGGGA GGGCCAACTA

      2530       2540       2550       2560       2570       2580
GAAGAAGCAC CTCCAACTAA TCCTTATAAT ACCCCCACAT TTGCAATTAA GAAAAAGGAC

      2590       2600       2610       2620       2630       2640
AAGAACAAAT GGAGAATGCT AATAGATTTT AGAGAACTAA ACAGGGTGAC TCAAGATTTC

      2650       2660       2670       2680       2690       2700
ACAGAAATTC AGCTAGGAAT TCCACACCCG GCAGGATTAG CCAAAAAGAA AAGGATTACT

      2710       2720       2730       2740       2750       2760
GTACTAGATG TAGGGGATGC CTACTTTTCC ATACCACTAC ATGAAGATTT TAGGCAATAT

      2770       2780       2790       2800       2810       2820
ACTGCATTTA CCCTACCATC AGTAAACAAT GCAGAGCCAG AAAAAAGATA TGTATATAAG

      2830       2840       2850       2860       2870       2880
GTCTTACCAC AAGGATGGAA AGGATCACCA GCAATCTTTC AATTCATGAT GAGGCAAATC

      2890       2900       2910       2920       2930       2940
TTAGAACCTT TCAGAAAAGC AAACCCAGAC GTCATTCTCA TCCAATACAT GGATGATATC

      2950       2960       2970       2980       2990       3000
TTAATAGCTA GTGACAGGAC GGGTTTAGAG CATGACAAAG TAGTCCTGCA ACTAAAAGAA

      3010       3020       3030       3040       3050       3060
CTTCTGAATG GCCTAGGGTT CTCTACCCCA GATGAGAAGT TCCAAAAGGA CCCTCCGTTT

      3070       3080       3090       3100       3110       3120
CAATGGATGG GCTATGAATT GTGGCCAACT AAATGGAAAC TGCAGAAAAT ACAATTACCT

      3130       3140       3150       3160       3170       3180
CAGAAAGAAA TATGGACAGT CAATGACATC CAAAAACTAG TAGGAGTTTT GAACTGGGCG

      3190       3200       3210       3220       3230       3240
GCGCAGATCT ATCCAGGGAT AAAAACCAAG CATTTATGTA AATTGATTAG AGGAAAAATG

      3250       3260       3270       3280       3290       3300
ACACTCACAG AGGAAGTACA GTGGACAGAG TTAGCAGAGG CAGAACTAGA AGAAAACAAA

      3310       3320       3330       3340       3350       3360
ATTATCTTAA GTCAGGAACA AGAGGGATCC TACTATCAGG AAGAAGAAGA ACTAGAAGCA

      3370       3380       3390       3400       3410       3420
ACAGTCATCA AAAGCCAAGA CAATCAGTGG GCATACAAAA TACACCAGGG AGAGAGGGTT

      3430       3440       3450       3460       3470       3480
CTAAAAGTAG GAAAGTATGC GAAGATAAAA AATACTCATA CCAATGGGGT CAGACTACTA

      3490       3500       3510       3520       3530       3540
GCACAAGTAG TCCAAAAAAT AGGAAAGGAA GCACTGGTCA TTTGGGGACG AGTGCCAAAA
```

Fig. 4

Sheet 4

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      3550        3560        3570        3580        3590        3600
TTTCACCTAC CGGTAGAGAG AGACACCTGG GAGCAATGGT GGGATAACTA CTGGCAAGTA

      3610        3620        3630        3640        3650        3660
ACATGGGTCC CAGAGTGGGA CTTCGTATCT ACCCCACCAC TGGTCAGGTT GACATTTAAC

      3670        3680        3690        3700        3710        3720
TTGGTAGGAG ATCCTATACC AGGCACAGAG ACCTTTTACA CAGATGGATC ATGCAATAGA

      3730        3740        3750        3760        3770        3780
CAGTCAAAAG AAGGAAAAGC AGGATATGTA ACAGATAGAG GGAGAGACAG GGTAAGAGTA

      3790        3800        3810        3820        3830        3840
TTAGAGCAAA CATCCAATCA GCAAGCAGAA CTAGAAGCCT TTGCGATGGC ACTGGCAGAC

      3850        3860        3870        3880        3890        3900
TCAGGTCCCA AGGTTAATAT CATAGTAGAC TCACAGTATG TAATGGGGAT AGTAGCAGGC

      3910        3920        3930        3940        3950        3960
CAACCAACAG AGTCAGAAAA TAGAATAGTA AACCAAATCA TTGAGGACAT GATAAAGAAA

      3970        3980        3990        4000        4010        4020
GAAGCAGTCT ATGTTGCATG GGTCCCAGCC CATAAAGGCA TAGGAGGAAA CCAGGAAGTA

      4030        4040        4050        4060        4070        4080
GACCATTTAG TAAGTCAGGG CATCAGACAA GTATTATTGC TGGAAAAGAT AGAGCCCCGT

      4090        4100        4110        4120        4130        4140
CAAGAAGAAC ACGAAAAATA TCATAGCAAT ATAAAAGAAC TAACCCATAA ATTTGGAATA

      4150        4160        4170        4180        4190        4200
CCCCAACTAG TGGCAAGACA GATAGTAAAC ACATGTGCCC AATGCCAACA GAAAGGAGAA

      4210        4220        4230        4240        4250        4260
GCCATACATG GGCAAGTAAA TGCAGAAATA GGCGTTTGGC AAATGGACTG CACACACTTA

      4270        4280        4290        4300        4310        4320
GAAGGAAAAA TCATTATAGT AGCAGTGCAT GTTGCAAGTG GATTCATAGA AGCAGAAGTC

      4330        4340        4350        4360        4370        4380
ATCCCACAGG AATCAGGAAG GCAGACAGCA CTCTTCCTAT TAAAACTGGC CAGTAGGTGG

      4390        4400        4410        4420        4430        4440
CCAATAACAC ACTTGCACAC AGACAATGGC CCCAACTTCA CTTCACAGGA AGTGAAGATG

      4450        4460        4470        4480        4490        4500
GTGGCATGGT GGATAGGTAT AGAGCAATCC TTTGGAGTAC CTTACAATCC ACAAAGCCAG

      4510        4520        4530        4540        4550        4560
GGAGTAGTAG AAGCAATGAA TCACCACCTA AAAAATCAGA TAAGTAGAAT TAGAGAACAG

      4570        4580        4590        4600        4610        4620
GCAAATACAA TAGAAACAAT AGTACTAATG GCAGTTCATT GCATGAATTT TAAAAGAAGG

      4630        4640        4650        4660        4670        4680
GGAGGAATAG GGGATATGAC CCCAGCAGAA AGACTAATTA ACATGATCAC CACAGAACAA

      4690        4700        4710        4720        4730        4740
GAAATACAAT TCCTCCAAAG AAAAAATTCA AATTTTAAAA AATTCCAGGT CTATTACAGA
```

Fig. 4


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      4750       4760       4770       4780       4790       4800
GAAGGCAGAG ATCAGCTGTG GAAAGGACCT GGAGAGCTAC TGTGGAAGGG AGACGGAGCA

      4810       4820       4830       4840       4850       4860
GTCATAGTCA AGGTAGGGGC GGACATAAAA GTAGTACCAA GAAGGAAGGC CAAGATTATC

      4870       4880       4890       4900       4910       4920
AGGGACTATG GAGGAAGGCA AGAACTGGAT AGTAGTTCCC ACCTGGAGGG TGCCAGGGAG

      4930       4940       4950       4960       4970       4980
GATGGAGAGG TGGCATAGCC TTGTCAAGCA CCTGAAGTAC AGAACAAAAG ACTTAGAGGA

      4990       5000       5010       5020       5030       5040
GGTGCGCTAT GTTCCCCATC ACAAGGTAGG ATGGGCATGG TGGACTTGCA GCAGGGTAAT

      5050       5060       5070       5080       5090       5100
ATTCCCACTA GAAGGAGAAA GTCATCTAGA GATACAGGCA TATTGGAACC TAACACCAGA

      5110       5120       5130       5140       5150       5160
AAAAGGATGG CTCTCCTCTC ATTCAGTAAG GTTAACCTGG TATACAGAAA AGTTCTGGAC

      5170       5180       5190       5200       5210       5220
AGATGTTACC CCAGACTGTG CAGACTCCCT AATACACAGC ACTTATTTCT CTTGCTTTAC

      5230       5240       5250       5260       5270       5280
GGCAGGTGAA GTAAGAAGAG CCATCAGAGG GGAAAAGTTA TTGTCCTGCT GCAACTACCC

      5290       5300       5310       5320       5330       5340
CCAAGCTCAT AAAGCACAGG TACCATCACT TCAATACCTA GCCCTAGTGG TAGTGCAACA

      5350       5360       5370       5380       5390       5400
AAATGGCAGA CCCCAGAGAA AGGGTGCCGC CAGGAAACAG TGGAGAAGAG ACCATTGGAG

      5410       5420       5430       5440       5450       5460
AGGCCTTCGA GTGGCTAGAC AGGACTATAG AAGCCTTAAA CAGGGAGGCA GTGAACCATC

      5470       5480       5490       5500       5510       5520
TGCCCCGAGA GCTCATTTTC CAGGTGTGGC AAAGGTCCTG GGCATATTGG CATGATGAAC

      5530       5540       5550       5560       5570       5580
AAGGGATGTC AACAAGTTAC ACAAAGTATA GATATTTGTG CA  TGCAG AAAGCTGTGT

      5590       5600       5610       5620       5630       5640
ATATACATTT CAAGAAGGGG TGCACTTGCC TGGGGAGAGG ACATGGCCCG GGAGGATGGA

      5650       5660       5670       5680       5690       5700
GACCAGGACC TCCCCCTCCT CCCCCTCCAG GTCTAGTCTA ATGACTGAAG CACCAACAGA

      5710       5720       5730       5740       5750       5760
GTTTCCCCCA GAAGATGGGA CCCCACGGAG AGAGCTAGGG AGTACCTGGG TAATAGAAAC

      5770       5780       5790       5800       5810       5820
TCTGAAGGAA ATCAAGGAAG AAGCCTTAAA ACATTTTGAT CCCTGCTTGC TAATTGCTCT

      5830       5840       5850       5860       5870       5880
TGGCAACTAT ATCTATAATA GACATGGAGA CACCCTTGAA GGAGCCAGAG AGCTCATTAG

      5890       5900       5910       5920       5930       5940
AGTCCTACAA CGAGCCCTCT TCGTGCACAT CAGAGCGGGA TGTGACCGCT CAAGAAAGGG
```

Fig. 4


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      5950        5960        5970        5980        5990        6000
CCAAACAAGG AGAAGAGCTC CTTGCCCAGC TGCACCGACC CCTAGAGGCA TGCACTAACT

      6010        6020        6030        6040        6050        6060
CATGCTATTG TAAGCAGTGC AGTTACCATT GCCAGCTGTG TTTCTTGAAA AAAGGGCTCG

      6070        6080        6090        6100        6110        6120
GGATATGGTA TGCGCGACAG GGCAGACGAA GAAGGACTCC AAGAAAAACT AAGACTCATC

      6130        6140        6150        6160        6170        6180
CGCCTCCTGC ATCAGATAAG TAAGTATGGA GCCTGGTAGG AATCAGCTGC TTGTTGCCAT

      6190        6200        6210        6220        6230        6240
TTTATTAACT AGTGCTTGCT TAATATATTG CAAACAATAT GTGACTGTTT TCTATGGCAT

      6250        6260        6270        6280        6290        6300
ACCCGCGTGG AGAAATGCAT CTATTCCCCT ATTTTGTGCA ACCAAAAATA GAGATACTTG

      6310        6320        6330        6340        6350        6360
GGGGACCATC CAGTGCTTGC CAGACAATGA TGATTATCAG GAAATAACCT TAAATGTGAC

      6370        6380        6390        6400        6410        6420
AGAAGCTTTT GATGCATGGG ATAATACAGT AACAGAACAA GCAATAGAAG ATGTCTGGAG

      6430        6440        6450        6460        6470        6480
ACTGTTTGAG ACATCAATAA AACCATGTGT CAAGTTGACG CCCCTATGTG TGGCGATGAA

      6490        6500        6510        6520        6530        6540
TTGTAATATA ACTTCAGGGA CTACCGCGAC CCCGAGTCCA CCAAACATTA CAATAATAGA

      6550        6560        6570        6580        6590        6600
TGAAAATTCT ACCTGTATAG GCGACAACAA CTGCACAGGA TTAGGGAAAG AAGAGGTGGT

      6610        6620        6630        6640        6650        6660
TGAGTGTGAG TTCAATATGA CGGGGCTAGA ACAAGATAAG AAAAGGAAGT ATAATGACGC

      6670        6680        6690        6700        6710        6720
ATGGTACTCA AGAGATGTGG TTTGTGACAA GACAAACGGA ACAGGCACAT GTTACATGAG

      6730        6740        6750        6760        6770        6780
ACATTGCAAC ACATCAGTCA TCAAAGAGTC ATGTGACAAG CACTATTGGG ATGCTATGAA

      6790        6800        6810        6820        6830        6840
GTTTAGATAC TGTGCACCAC CGGGTTTTGC CCTACTAAGA TGCAATGATA CCAACTATTC

      6850        6860        6870        6880        6890        6900
AGGCTTTGAA CCTAAGTGCT CTAAAGTAGT AGCTGCTTCA TGCACAAGGA TGATGGAAAC

      6910        6920        6930        6940        6950        6960
GCAAACTTCT ACTTGGTTTG GCTTTAATGG CACTAGAGCA GCAGATAGAA CATATATCTA

      6970        6980        6990        7000        7010        7020
TTGGCATGGT AAGGATAATA GGACTATCAT TAGCTTAAAC AGGTATTATA ATCTCACAAT

      7030        7040        7050        7060        7070        7080
GCATTGTAAG AGACCAGGAA ATAAGACAGT TGTACCAATA ACACTTATGT CAGGGCGAAG

      7090        7100        7110        7120        7130        7140
GTTTCACTCT CGGCCAGTCT ACAACAAAAA ACCTGGGCAG GCATGGTGTT GGTTTCAAGG
```

Fig. 4


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      7150        7160        7170        7180        7190        7200
CAACTGGATA GAAGCCATGC GGGAGGTGAA GCAAACCCTT GCAAAACATC CCAGGTACGG

      7210        7220        7230        7240        7250        7260
AGGAACAAAT GATACAGGAA AAATTAACTT TACGAAGCCA GGAATAGGTT CAGACCCAGA

      7270        7280        7290        7300        7310        7320
AGTGACATAC ATGTGGACTA ACTGCAGAGG AGAATTTCTC TACTGTAATA TGACTTGGTT

      7330        7340        7350        7360        7370        7380
CCTCAATTGG GTAGAAAATA AGACGAACCA AACACACGGC AACTATGCGC CATGCCATAT

      7390        7400        7410        7420        7430        7440
AAGGCAGATA ATTAACACCT GGCATAAGGT AGGGACAAAT GTATATTTGC CTCCTAGGGA

      7450        7460        7470        7480        7490        7500
AGGGGAGTTG ACCTGCAATT CAACAGTAAC CAGCATAATT GCTAACATTG ACTCAGATGG

      7510        7520        7530        7540        7550        7560
AAATCAGACC AACATTACCT TTAGTGCAGA AGTGGCAGAA CTGTACCGAT TAGAATTGGG

      7570        7580        7590        7600        7610        7620
GGACTACAAA TTGATAGAAG TAACACCAAT TCCGTTCGCA CCTACAAAAG AGAAAAGATA

      7630        7640        7650        7660        7670        7680
TTCCTCGGCT CCAGTGAGGA ACAAAAGAGG TGTGTTCGTG CTAGGGTTCT TGGGTTTTCT

      7690        7700        7710        7720        7730        7740
CGCAGCAGCA GGTTCTGCAA TGGGCGGCNC GTCCTTGACG CTGTCGGCTC AGTCCCGGAC

      7750        7760        7770        7780        7790        7800
TTTACTGGCC GGGATAGTGC AGCAACAGCA ACAGCTGTTG GACGTGGTCA AGAGACAACA

      7810        7820        7830        7840        7850        7860
AGAAATGTTG CGATTGACCG TCTGGGGAAC GAAAAATCTC CAGGCAAGAG TCACTGCTAT

      7870        7880        7890        7900        7910        7920
CGAGAAATAC TTAAAGGACC AGGCACAGCT AAATTCATGG GGATGTGCGT TTAGGCAGGT

      7930        7940        7950        7960        7970        7980
CTGCCACACT ACTGTACCAT GGGTAAATGA CTCCTTAACA CCTGACTGGA ACAATATGAC

      7990        8000        8010        8020        8030        8040
ATGGCAGGAA TGGGAAAAAC GAGTCCACTA CCTAGAGGCA AATATCAGTC AAAGTTTAGA

      8050        8060        8070        8080        8090        8100
ACAGGCACAA ATTCAACAAG AAAAGAATAT GTATGAACTA CAAAAACTAA ATAGCTGGGA

      8110        8120        8130        8140        8150        8160
TGTCTTTGGC AACTGGTTTG ATTTGACCTC CTGGATCAAA TATATTCAAT ATGGAGTTTA

      8170        8180        8190        8200        8210        8220
TATAGTAGTA GGAATAATAG GTTTAAGAAT AGCCATATAT ATAGTGCAAT TGTTAAGTAG

      8230        8240        8250        8260        8270        8280
ACTTAGAAAG GGCTATAGGC CTGTTTTCTC CTCCCCCCCC GGTTATCTCC AACAGATCCA

      8290        8300        8310        8320        8330        8340
TATCCACACG GACAGGGGAC AGCCAGCCAA CGAAGAAACA GAAGAAGACG CCGGAGACGA
```

Fig. 4


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      8350        8360        8370        8380        8390        8400
CAGTGGTTTC GGCTTGTGGC CTTGGCCACT AAACTACATA CAATTCCTGA TCCACCTACT

      8410        8420        8430        8440        8450        8460
GACTCGCCTC TTGACCGGGC TATACAACAG CTGCAGGGGC TTACTATCCA AGAACTCCCC

      8470        8480        8490        8500        8510        8520
GACCCGCCGA CTGATCTCCC AGAGTCTAAC AGCAATCAGG GACTGGCTGA GACTTAAGGC

      8530        8540        8550        8560        8570        8580
GGCCTACCTG CAATATGGGT GCGAGTGGAT CCAAGAAGCG TTCCGAGCAT TCGCAAGGAC

      8590        8600        8610        8620        8630        8640
TGCGAGAGAG ACTATTGCGG GCGCGTGGAG GGGGTTATGT GAAGCAGCGC AACGCATCGG

      8650        8660        8670        8680        8690        8700
CAGGGGAATC CTCGCAGTCC CAAGAAGGAT CAGGCAGGGA CCACAAATCC CCCTCCTCTC

      8710        8720        8730        8740        8750        8760
AGGGACAGCA GTATCAGCAG GGAGAGTTCA TGAACACCCC ATGGAGAACC CCAGCAGCAA

      8770        8780        8790        8800        8810        8820
TAGGGCAGAA AAATTCATAT AAGCAGCAAA ATATGGATGA TGTAGATTCT GATGATGATG

      8830        8840        8850        8860        8870        8880
ACCTAGTGGG AGTTCCTGTT ATGCCAAGAG TACCGCTGAG AGAAATGACC TATAAACTGG

      8890        8900        8910        8920        8930        8940
CAATAGATAT GTCACATTTT ATAAAAGAAA AAGGAGGACT GGAAGGGATA TTTTACAGTA

      8950        8960        8970        8980        8990        9000
GGGAGAGACA TAGAATCCTA GACTTGTTCC TAGAAAAGGA GGAAGGGATA ATACCAGATT

      9010        9020        9030        9040        9050        9060
GGCAGAATTA TACTCATGGG CCAGGAACAA GGTACCCAAT GTACTTCGGG TGGCTGTGGA

      9070        9080        9090        9100        9110        9120
AACTAGTACC AGTAGACATC TCACAAGAGG CAGAGGAAGT AGAGACCAAC TGCTTAGTAC

      9130        9140        9150        9160        9170        9180
ACCCAGCACA AACAAGCAGA TATGATGACG AGCATGGGGA GACACTAGTT TGGCGGTTTG

      9190        9200        9210        9220        9230        9240
ACCCCATGCT GGCCTATAGT TACAAGGCCT TCATTCTGCA CCCAGAAGAA TTTGGGCACA

      9250        9260        9270        9280        9290        9300
AGTCAGGATT GCCAGAGAAA GAGTGGAAGG CAAAACTGAA AGCAAGAGGG ATACCATATA

      9310        9320        9330        9340        9350        9360
GTGAATAACA GGAACAACCA TACTTGGTCA GGGCAGGAAA TAGCTACTAA GAACAGCTGA

      9370        9380        9390        9400        9410        9420
GACTGCAGGG ACTTTCCAGA AGGGGCTGTA ACCAAGGGAG GGACATGGGA GGAGCTGGTG

      9430        9440        9450        9460        9470
GGGAACGCCC TCATATTCTC TGTATAAATG TACCCGCTTC TTGCATTGTA TTC
```

Fig. 5 Sheet 1

Partial nucleotide sequences of HIV-D205
(corresponding to clone HIV-2 A7.1 of Fig. 2);

HIV-D205; corresponding to pos. 8942-9255 in HIV-2 ROD; homology 71.6 %

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        10          20          30          40          50          60
TGGAAGGGAT GTATTATAGT GAGAGAAGAC ACAGAATATT AGACACATAT TTTGAGAATG

        70          80          90         100         110         120
AAGAAGGCAT TGTGTCTGGC TGGCAAAACT ATACTCATGG GCCAGGGATA AGGCATCCCA

       130         140         150         160         170         180
AATACTTTGG TTGGCTGTGG AAGCTGGTAC CAGTAGAGGT GCCAGCAGCG ACCCGAGAGG

       190         200         210         220         230         240
AGGAGGAAAC CCATTGCCTA ATGCACCCGG CACAGATCTC CTCATGGGAT GACATCCATG

       250         260         270         280         290         300
GGGAGACTCT TATCTGGCAG TTTGATTCCC TCCTGGCATA TGATTATGTG GCTTTCAATA

       310
GGTTTCCAGA AGAGTTT
```

HIV-D205, corresponding to position 718-2510 in HIV-2ROD; homology 78.6 %

```
        10          20          30          40          50          60
AAAAAATTCT TAAAGTCTTA GCTCCATTAG TACCAACAGG GTCAGAAAAT TTAAAAAGCC

        70          80          90         100         110         120
TTTTTAATAT CGTCTGCGTC ATTTTTTGCC TGCACGCAGA AGAGAAAGTG AAAGATACAG

       130         140         150         160         170         180
AGGAAGCAAA AAAGATAGCA CAGAGACATC TAGCGGCGGA CACAGAAAAA ATGCCAGCTA

       190         200         210         220         230         240
CAAATAAACC AACAGCACCA CCTAGCGGCG GAAATTATCC AGTGCAGCAA CTGGCTGGCA

       250         260         270         280         290         300
ACTACGTCCA CCTGCCGCTA AGCCCCCGAA CCTTAAATGC TTGGGTAAAG TTAGTAGAAG

       310         320         330         340         350         360
AAAAGAAGTT CGGGGCAGAA GTAGTACCAG GATTTCAGGC ACTATCAGAA GGATGCACCC

       370         380         390         400         410         420
CTTATGATAT AAATCAGATG CTAAATTGTG TAGGAGAACA TCAGGCAGCC ATGCAAATTA

       430         440         450         460         470         480
TTAGAGAAAT AATCAATGAG GAAGCAGCAG ACTGGGACCA GCAACACCCG TCACCAGGCC
```

Fig. 5 Sheet 2

```
       490         500         510         520         530         540
CAATGCCGGC AGGACAACTT AGGGACCCAA GAGGGTCAGA TATAGCAGGA ACCACCAGCA

       550         560         570         580         590         600
CAGTAGAGGA ACAGATACAG TGGATGTACA GGGCCCAAAA TCCTGTCCCA GTGGGAAACA

       610         620         630         640         650         660
TTTATAGAAG ATGGATTCAA TTAGGATTGC AGAAATGTGT CCGAATGTAC AATCCTACCA

       670         680         690         700         710         720
ACATATTAGA CATAAAGCAG GGACCAAAGG AGCCCTTCCA AAGCTATGTA GATAGATTCT

       730         740         750         760         770         780
ACAAAAGCTT ACGGGCAGAA CAAACAGACC CAGCAGTGAA AAATTGGATG ACACAAACAC

       790         800         810         820         830         840
TGCTGATTCA GAATGCTAAC CCAGATTGCA AGTTAGTGCT TAAGGGCTTG GGAATGAATC

       850         860         870         880         890         900
CCACCTTAGA GGAAATGCTA ACGGCCTGCC AAGGGATAGG AGGCCCAGGG CAGAAGGCAA

       910         920         930         940         950         960
GGCTAATGGC CGAAGCCTTA AAAGAGGCCC TAACACCTGC ACCCATACCG TTTGCTGCCG

       970         980         990        1000        1010        1020
TTCAACAAAA AGCAGGGAAG AGAGGGACAG TGACATGCTG GAACTGTGGC AAACAGGGAC

      1030        1040        1050        1060        1070        1080
ACACAGCCAG GCAATGCAGG GCCCCTAGAA GACAGGGATG CTGGAAATGT GGAAAAACAG

      1090        1100        1110        1120        1130        1140
GACACATCAT GTCAAAATGC CCAGAAAGAC AGGCGGGTTT TTTAGGGTTA GGACCCTGGG

      1150        1160        1170        1180        1190        1200
GAAAGAAGCC TCGCAACTTC CCCATGACCC AAGTGCCTCA GGGAGTGACA CCATCTGCAC

      1210        1220        1230        1240        1250        1260
CCCCGATGAA CCCAGCAGAG GGCATGACAC CTCGGGGGGC GACACCATCT GCGCCCCCTG

      1270        1280        1290        1300        1310        1320
CAGATCCAGC AGTGGAGATG CTGAAAAGTT ACATGCAGAT GGGGAGACAA CAGAGAGAGA

      1330        1340        1350        1360        1370        1380
GCCGAGAGAG ACCCTACAAG GAGGTGACAG AGGATTTGCT GCACCTCAAT TCTCTCTTTG

      1390        1400        1410        1420        1430        1440
GAGAAGACCA GTAGTCAAAG CATGTATCGA GGGTCAGTCA GTAGAAGTAT TACTAGACAC

      1450        1460        1470        1480        1490        1500
AGGAGTTGAC GACTCAATAG TAGCAGGGAT AGAATTAGGT AGCAATTACA CCCCAAAAAT

      1510        1520        1530        1540        1550        1560
AGTAGGAGGG ATAGGAGGGT TCATAAATAC CAAAGAATAC AAAGATGTAG AAATAGAAGT

      1570        1580        1590        1600        1610        1620
AGTGGGAAAA AGAGTAAGGG CAACTATAAT GACAGGAGAT ACCCCAATAA ACATTTTTGG
```

Fig. 5 Sheet 3

```
      1630        1640        1650        1660        1670        1680
CAGAAATATT TTAAATACCT TGGGCATGAC TTTAAATTTC CCAGTGGCAA AGGTAGAACC

      1690        1700        1710        1720        1730        1740
AGTAAAAGTT GAGTTAAAAC CTGGAAAAGA TGGGCCAAAG ATCAGACAAT GGCCTCTATC

      1750        1760        1770        1780        1790
CAGGGAAAAG ATACTAGCCC TCAAAGAAAT CTGTGAAAAA ATGGAAAAGG
```

HIV-D205, corresponding to position 2877-7293 in HIV-2ROD; homology 75.1 %.

```
        10          20          30          40          50          60
AGGTATTAGA TCCTTTTAGA AAGGCCAACA GCGATGTCAT TATAATTCAG TACATGGATG

        70          80          90         100         110         120
ACATCCTTAT AGCAAGTGAC AGAAGTGATC TGGAGCACGA CAGGGTAGTG TCCCAACTAA

       130         140         150         160         170         180
AAGAGTTATT AAATGACATG GGATTCTCTA CCCCAGAAGA AAAGTTCCAA AAAGACCCTC

       190         200         210         220         230         240
CGTTCAAATG GATGGGTTAT GAGCTCTGGC CAAAAAAGTG GAAACTGCAA AAAATACAAC

       250         260         270         280         290         300
TGCCAGAAAA AGAAGTTTGG ACAGTGAATG CAATTCAAAA ACTGGTAGGA GTATTAAACT

       310         320         330         340         350         360
GGGCAGCTCA ACTCTTTCCT GGAATTAAGA CAAGGCACAT ATGCAAACTA ATTAGGGGAA

       370         380         390         400         410         420
AGATGACCCT AACAGAAGAA GTACAGTGGA CAGAACTAGC AGAAGCAGAG CTACAGGAGA

       430         440         450         460         470         480
ATAAAATCAT CTTAGAACAG GAACAAGAAG GATCCTACTA CAAGGAAAGG GTACCGCTAG

       490         500         510         520         530         540
AAGCAACAGT ACAGAAAAAC CTAGCAAATC AGTGGACATA CAAAATTCAT CAGGGAAATA

       550         560         570         580         590         600
AAGTCCTAAA AGTAGGAAAA TATGCAAAGG TTAAAAACAC GCACACCAAC GGGGTAAGAC

       610         620         630         640         650         660
TACTGGCACA TGTAGTTCAG AAAATAGGCA AAGAAGCCCT AGTCATCTGG GGAGAGATAC

       670         680         690         700         710         720
CAGTGTTCCA TCTGCCAGTA GAAAGAGAGA CATGGGACCA GTGGTGGACA GATTACTGGC

       730         740         750         760         770         780
AAGTAACCTG GATCCCAGAG TGGGACTTTG TCTCGACCCC ACCATTAATA AGACTAGCCT

       790         800         810         820         830         840
ACAACCTAGT CAAAGACCCC CTAGAAGGGA GAGAAACCTA CTACACAGAT GGGTCCTGCA
```

Fig. 5


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       850        860        870        880        890        900
ATAGAACCTC AAAGGAAGGA AAAGCAGGAT ATGTCACTGA CAGGGGAAAA GATAAGGTTA

       910        920        930        940        950        960
AAGTGTTAGA ACAGACAACA AACCAACAAG CAGAACTTGA AGCATTTGCA TTAGCATTAA

       970        980        990       1000       1010       1020
CAGACTCAGA ACCACAAGTT AACATCATAG TAGATTCACA ATATGTCATG GGAATAATAG

      1030       1040       1050       1060       1070       1080
CTGCACAGCC AACAGAAACA GAATCACCAA TAGTAGCAAA AATAATTGAA GAAATGATCA

      1090       1100       1110       1120       1130       1140
AAAAAGAGGC AGTATATGTA GGATGGGTAC CAGCTCACAA GGGACTGGGT GGTAATCAGG

      1150       1160       1170       1180       1190       1200
AAGTAGACCA CCTAGTAAGT CAAGGAATCA GACAGGTCTT GTTCCTAGAA AAAATAGAAC

      1210       1220       1230       1240       1250       1260
CAGCCCAGGA AGAGCATGAA AAATATCATG GCAATGTAAA AGAACTGGTC CATAAATTCG

      1270       1280       1290       1300       1310       1320
GAATTCCACA ATTAGTGGCA AAACAGATAG TAAATTCCTG TGATAAATGC CAACAAAAAG

      1330       1340       1350       1360       1370       1380
GGGAAGCTAT TCATGGACAG GTAAATGCAG ACCTAGGGAC ATGGCAGATG GACTGTACAC

      1390       1400       1410       1420       1430       1440
ATTTAGAAGG AAAAATTATA ATAGTGGCAG TCCATGTAGC CAGTGGGTTT ATAGAAGCAG

      1450       1460       1470       1480       1490       1500
AGGTAATACC CCAAGAGACA GGAAGACAGA CAGCTCTCTT CCTACTAAAG TTGGCCAGCA

      1510       1520       1530       1540       1550       1560
GATGGCCTAT CACACACCTA CACACAGACA ACGGTGCCAA CTTCACCTCA CCAAGTGTAA

      1570       1580       1590       1600       1610       1620
AGATGGTAGC CTGGTGGGTA GGAATAGAAC AAACTTTTGG AGTACCCTAT AACCCACAAA

      1630       1640       1650       1660       1670       1680
GTCAAGGAGT AGTGGAAGCA ATGAACCATC ACCTGAAAAA TCAAATAGAC AGACTCAGAG

      1690       1700       1710       1720       1730       1740
ACCAAGCAGT ATCAATAGAG ACAGTTGTAC TAATGGCAAC TCACTGCATG AATTTTAAAA

      1750       1760       1770       1780       1790       1800
GAAGGGGAGG AATAGGGGAT ATGACCCCTG CAGAAAGACT AGTTAACATG ATAACCACAG

      1810       1820       1830       1840       1850       1860
AGCAAGAAAT ACAGTTCTTC CAAGCAAAAA ATTTAAAATT TCAAAATTTC CAGGTCTATT

      1870       1880       1890       1900       1910       1920
ACAGAGAAGG CAGAGATCAA CTCTGGAAGG GACCTGGTGA ACTATTGTGG AAAGGGGAAG

      1930       1940       1950       1960       1970       1980
GAGCAGTCAT CATAAAGGTA GGGACAGAAA TCAAAGTAGT ACCCAGGAGA AAAGCAAAAA
```

Fig. 5


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      1990        2000        2010        2020        2030        2040
TTATAAGGCA CTATGGAGGA GGAAAAGGAT TGGATTGTAG TGCCGACATG GAGGATACCA

      2050        2060        2070        2080        2090        2100
GGCAGGCTAG AGAGATGGCA CAGTCTGATT AAGTATCTTA AGTATAGAAC AGGAGAGTTG

      2110        2120        2130        2140        2150        2160
CAACAGGTCT CTTATGTCCC TCACCACAAG GTAGGATGGG CTTGGTGGAC TTGCAGTAGA

      2170        2180        2190        2200        2210        2220
ATAATATTTC CCCTAAACAA AGGAGCATGG CTAGAAGTCC AAGGATATTG GAACCTAACC

      2230        2240        2250        2260        2270        2280
CCAGAAAGGG GATTCTTGAG CTCCTATGCT GTAAGACTAA CATGGTATGA GAGGAACTTT

      2290        2300        2310        2320        2330        2340
TATACAGATG TAACACCTGA TGTGGCAGAC CAGCTACTGC ATGGGTCTTA TTTCTCTTGC

      2350        2360        2370        2380        2390        2400
TTTTCAGCCA ATGAAGTAAG GAGAGCCATC AGGGGAGAAA AGATATTGTC CTACTGCAAC

      2410        2420        2430        2440        2450        2460
TATCCATCAG CTCACGAAGG GCAGGTACCA AGCTTACAGT TTCTAGCCCT AAGGGTCGTA

      2470        2480        2490        2500        2510        2520
CAGGAAGGAA AAAATGGATC CCAGGGAGAG AGTGCCACCA GGAAACAGCG ACGAAGAAAC

      2530        2540        2550        2560        2570        2580
AGTAGGAGAA GCATTCGCTT GGCTAGAAAG AACAATAACA GAGCTCAACA GGGTAGCGGT

      2590        2600        2610        2620        2630        2640
CAACCATTTG CCCCGAGAAC TTATTTTCCA GGTCTGGCAG AGGTCTTGGG CATACTGGCG

      2650        2660        2670        2680        2690        2700
TGAGGAACAG GGCATGTCAA TTAGCTATAC CAAATATAGA TACTTGTTGC TAATGCAGAA

      2710        2720        2730        2740        2750        2760
AGCAATGTTT GTGCACTATA CAAAGGGCTG TAGGTGCCTG CAGGAGGGCC ATGGGCCAGG

      2770        2780        2790        2800        2810        2820
GGGATNGAGA TCAGGACCTC CTCCTCCTCC TCCCCCAGGC CTGGCCTAAT GGCAGAAGCA

      2830        2840        2850        2860        2870        2880
GCCCCAGAGA TCCCTCCAGA GAACGAGAAC CCACAAAGAG AACCGTGGGA AGAGTGGATA

      2890        2900        2910        2920        2930        2940
GGGGAGATCC TGGAGGAAAT AAAGCAAGAA GCCTTAAAGC ATTTTGATCC TCGCTTGCTA

      2950        2960        2970        2980        2990        3000
ACTGCGCTTG GTAACTTTAT CTACAGTAGG CATGGAGATA CCCTTGCAGG AGCAGGAGAG

      3010        3020        3030        3040        3050        3060
CTCATTAAAA TCCTCCAACG AGCNCTCTTC CTCCACTTCA GAGCCGGTTG TCAACACTCA

      3070        3080        3090        3100        3110        3120
AGGATTGGAC AATCAGGGGG AGGAAATCCT CTCTCAACTA TACCGCCCCC TTAAGGCATG
```

Fig. 5


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      3130        3140        3150        3160        3170        3180
CGATAATACA TGCTACTGTA AGAAATGCTG CTACCATTGC CAGCTTTGTT TTCTTAAAAA

      3190        3200        3210        3220        3230        3240
GGGTCTTGGG ATATGTTATG ACCGCTCGAG AAGGAGATCT GCAAAAAGAG CTAAGACTAC

      3250        3260        3270        3280        3290        3300
TGCACCTTCT GCACCAGACA AGTGAGTATG GCATATTTTA GCAGCCGCCT GCCTATTGCG

      3310        3320        3330        3340        3350        3360
CTCCTGCTTA TAGGTATCAG TGGGTTTGTA TGTAAACAAT ATGTTACTGT CTTCTATGGC

      3370        3380        3390        3400        3410        3420
ATACCCGCAT GGAGGAACGC AACAGTTCCC CTCATTTGTG CAACCACAAA CAGAGACACC

      3430        3440        3450        3460        3470        3480
TGGGGAACTG TACAGTGTCT CCCAGACAAT GGTGACTACA CTGAGATCAG GCTAAACATA

      3490        3500        3510        3520        3530        3540
ACAGAGGCTT TTGATGCATG GGATAATACA GTGACACAAC AGGCAGTAGA TGATGTGTGG

      3550        3560        3570        3580        3590        3600
AGACTCTTTG AAACCTCCAT AAAACCATGT GTCAAACTAA CCCCACTGTG TGTGGCAATG

      3610        3620        3630        3640        3650        3660
AACTGTAGTA AAACCGAAAC AAACCCAGGG AATGCCAGTA GTACTACCAC CACTAAGCCT

      3670        3680        3690        3700        3710        3720
ACTACCACCT CTCGTGGGCT GAAAACGATT AACGAAACAG ACCCATGCAT AAAAAATGAC

      3730        3740        3750        3760        3770        3780
AGCTGCACAG GACTAGGAGA AGAGGAAATA ATGCAATGTA ATTTTAGTAT GACGGGACTA

      3790        3800        3810        3820        3830        3840
AGAAGAGATG AGCTAAAACA ATATAAAGAC ACCTGGTACT CAGAAGATTT AGAGTGTAAT

      3850        3860        3870        3880        3890        3900
AATACCAGGA AGTAATACCA GCAGTGCTAT ATAAGAACCT GCAACACAAC AATTATCCAA

      3910        3920        3930        3940        3950        3960
GAGTCATGTG ACAAACATTA TTGGGACAGC TTAAGGTTTA GGTATTGTGC TCCCCCGGGG

      3970        3980        3990        4000        4010        4020
TTTTTTCTAC TAAGATGTAA TGATACCAAC TATTCAGGCT TCATGCCCAA CTGCAGTAAG

      4030        4040        4050        4060        4070        4080
GTAGTAGCGT CCTCCTGCAC AAGAATGATG GAAACACAGT CCTCTACATG GTTTGGCTTC

      4090        4100        4110        4120        4130        4140
AATGGTACAA GGGCAGAGAA CAGGACATAT ATATATTGGC ATGAAAAAGA CAATAGGACC

      4150        4160        4170        4180        4190        4200
ATCATAAGCT TAAATACATA CTATAATTTG TCAATACACT GTAAGAGGCC AGGAAACAAG

      4210        4220        4230        4240        4250        4260
ACGGTTGTAC CAATAAGAAC CGTGTCAGGA CTACTTTTCC ATTCACAGCC TATCAATAAG
```

Fig. 5


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      4270       4280       4290       4300       4310       4320
AGACCCAGAC AAGCTTGGTG CTGGTTTAAG GGAAACTGGA CAGAAGCCAT AAAGGAGGTG

      4330       4340       4350       4360       4370       4380
AAAAGGACCA TCATAAAACA TCCCAGGTAT AAAGGAGGTG CAAAAAATAT CACAAGCGTA

      4390       4400       4410
AAGTTAGTAT CAGAACATGG AAAAGGTTCA GATC
```

Fig. 6

Sequence homology between HIV-D194 and HIV-2ROD in (%), separately for the functional elements.
The env region is not included because of the very much unrelated internal region shown in Fig. 3).

(nt ho = nucleotide homology, AA ho = amino acid homology)

	Position	nt ho	AA ho
R	1-173	96.0	
U5	174-299	94.4	
5'-untransl.	300-545	93.5	
gag	546-2114	88.1	89.1
pol	1829-4939	88.7	89.6
vif	4869-5516	88.7	82.9
vpx	5344-5682	86.7	89.4
vpr	5682-5999	83.0	74.5
tat ex 1	5845-6140	84.5	73.5
rev ex 1	6071-6140	87.1	82.6
tat ex 2	8307-8403	80.4	75.0
rev ex 2	8307-8539	78.5	70.0
nef	8557-9327	82.6	73.9
U3	8942-9496	85.4	

Fig. 7

Sequence homology of HIV-$2_{D205,7}$ compared to the HIV/SIV group (gene level; nt / aa)

		HIV-$2_{D205,7}$					
gene	position	HIV-2_{ROD}	HIV-2_{NIHZ}	HIV-2_{D194}	SIV_{MAC}	SIV_{AGM}	HIV-1_{BRU}
gag	720-1826	80.5 / 85.6					
gag	1860-2114	83.1 / 77.6					
pol	1859-2510	80.2 / 72.5					
pol	2877-4948	78.3 / 83.5					
protease	2084-2381	84.0 / 81.0	83.0 / 84.8	84.8 / 86.8	76.3 / 83.8	57.8 / 47.1	60.4 / 48.5
vif	4869-5516	72.0 / 68.5	70.9 / 67.9	72.4 / 66.5	71.8 / 60.6	53.8 / 34.7	47.9 / 33.0
vpx	5344-5682	76.1 / 74.1	73.5 / 68.1	74.6 / 77.9	75.2 / 77.0	50.8 / 34.7	
vpr	5682-5999	78.8 / 69.8	77.7 / 69.8	74.2 / 59.4	78.9 / 76.4		51.9 / 47.3
tatex1	5845-6140	78.4 / 66.3	79.1 / 68.4	74.7 / 63.3	81.1 / 66.3	33.1 / 38.1	33.6 / 34.0
revex1	6071-6140	67.1 / 61.9	68.6 / 60.9	67.1 / 52.2	70.0 / 60.9	45.5 / 28.6	38.2 / 40.4
nef	8557-9255	72.1 / 69.5					
env	6147-7293	70.0 / 67 0					

Fig. 8

Nucleotide sequence comparison of HIV-2_{D205} with HIV and SIV strains (in % homology)

HIV-2_{D205} position	HIV-2_{ROD}	HIV-2_{NIHZ}	HIV-2_{D194}	SIV_{MAC}	SIV_{AGM}	HIV-1_{BRU}
8942-9255	71.6	77.0	68.8	66.4	56.3	54.7
718-1825	80.5	80.8	80.3	79.1	65.1	63.8
1859-2510	80.2	74.6	75.0	78.8	55.6	56.9
2877-7293	75.1	74.8	75.4	74.0	58.0	54.6
Total	75.9	75.9	75.9	75.0	58.9	56.4

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(54) HIV-2 virus variants.

(57) HIV-2 virus variants, namely virus HIV D194 and virus HIV D205, which can be cloned from the corresponding virus isolate HIV D194 (ECACC V 87122303) or from the infected cell line HUT 194 (ECACC V 87122306) or from the virus isolate HIV D205 (ECACC V 87122304), respectively, and their RNA or RNA-fragments and DNA and DNA-fragments derived therefrom and/or proteins and the use thereof for diagnostics and therapy.

EP 0 347 365 A3

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EUROPEAN SEARCH REPORT

Application Number

EP 89 71 0057

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	EP-A-0 269 520 (INSTITUT PASTEUR) * The whole document *	1-26	C 12 N 7/00 C 12 N 15/00 C 07 K 15/04
X	NATURE, vol. 328, 6th August 1987, pages 548-550; S.K. ARYA et al.: "New human and simian HIV-related retroviruses process functional transactivator (tat) gene" * The whole article *	9,10,21	G 01 N 33/569 A 61 K 39/21 A 61 K 39/395 C 12 N 5/00
P,X	EP-A-0 327 801 (DEUTSCHES PRIMATENZENTRUM GmbH) * The whole document *	9,10, 21-23	
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TECHNICAL FIELDS SEARCHED (Int. Cl.5)
C 12 N C 07 K

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	07 February 91	CUPIDO M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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